CASE REPORT

Amyotrophic Lateral Sclerosis with Frontotemporal Dementia in the Presence of C9orf72 Repeat Expansion—A Case Report

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ABSTRACT

Amyotrophic lateral sclerosis and frontotemporal dementia are significant neurodegenerative illnesses with possible genetic predispositions. The C9orf72 gene and the GGGGCC repeat expansions of it are reported to have a causative role in the expression of these conditions. We report a case of a patient with autosomal dominant amyotrophic lateral sclerosis and frontotemporal dementia (ALS-FTD) in the presence of C9orf72 repeat expansion. We believe our case further supports the theory that the presence of C9orf72 repeat expansion in patients with a family history of amyotrophic lateral sclerosis and/or frontotemporal dementia significantly increases their risk of developing either or both diseases. The development of antisense oligonucleotides that might target GGGGCC RNA sequences theoretically may have a therapeutic role in mitigating the clinical expression of these illnesses.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are significant neurodegenerative illnesses. There is ongoing clinical research into the genetic predispositions toward these conditions. The presence of the C9orf72 gene and the GGGGCC repeat expansions is thought to be responsible for the familial form of these diseases. We report a case of a patient with autosomal dominant ALS and FTD (ALS-FTD) in the presence of C9orf72 repeat expansion.

CLINICAL VIGNETTE

A 72-year-old, right-handed, Caucasian woman presented with a one-year history of progressively slurred speech, dysphagia, facial droop, and limited social interaction. Her family reported speech difficulties and slowing of motor activities, especially when standing up or climbing stairs.

The patient was a social person, but her interaction with others was reduced because of speech dysfunction. Swallowing was difficult

for both liquids and solids. The patient denied any problems with memory, and she was able to take care of all household activities including cooking, buying groceries, and managing finances. She denied numbness, weakness, incontinence, visual changes, or falling. She never smoked tobacco and denied alcohol or drug abuse. Her past medical history was significant for diabetes, hyperlipidemia, and hypertension. Current medications included metformin, simvastatin, and triamterene-hydrochlorothiazide. One of her children was diagnosed with amyotrophic lateral sclerosis at the age of 43 years and died two years later, but her other three adult children had no evident neurological disease. Her father developed Parkinson's disease at 70 years of age.

On examination, the patient's mental status was unremarkable. Spastic dysarthria, left nasolabial fold flattening, and tongue fasciculations were noted. Motor strength was normal in the limbs, but she was slow to rise from a sitting position. A bilateral resting tremor was noted in the upper extremities. Deep tendon reflexes were 1+ bilaterally, with down-going plantars. Sensation and coordination was intact. Gait was slow, with reduced arm swing.

Over the next few months, the patient's swallowing and speech further deteriorated. Social and functional ability was declining. She communicated by writing and became wheelchair-bound within eight months, requiring tube feeds and respiratory assistance during sleep.

Magnetic resonance imaging of the brain revealed diffuse cortical atrophy with ventricular dilatation. The neuropsychiatry evaluation was consistent with frontotemporal dementia. An ultrasound documented fasciculation in the genioglossus bilaterally and in right masseter. A concentric needle electromyography confirmed the presence of fasciculations in the tongue. Genetic testing revealed hexanucleotide repeat expansion mutation on chromosome 9, open reading frame 72(C9orf72) ">44 and 8 repeats" (>30 is pathogenic) consistent with autosomal dominant ALS-FTD.

DISCUSSION

Five to 10 percent of the diagnoses of ALS are familial in nature.[1,2] Approximately 40 percent of the diagnoses of ALS are secondary to C9orf72 repeat expansion. The frequency of repeat expansion is higher in Finnish populations, with speculation that this mutation is of northern European origin.

Our described case describes a patient with autosomal dominant ALS and FTD (ALS-FTD). The ALS, which appeared in her son at the age of 43 years, might have been secondary to genetic anticipation; had he lived beyond age 45, he may have developed FTD.

By genetic linkage, locus on 9p21 was documented in a high proportion of patients with concurrent ALS and FTD.[1,2] The gene associated with that locus is identified as a GGGGCC repeat expansion. The hexanucleotide repeat expansion of GGGGCC in the noncoding region of the C9orf72 gene has been implicated in familial and sporadic ALS and FTD. It is considered to be the most common genetic cause of familial ALS and/or FTD.[3] The mechanism is suspected to be by toxic gain-of-function secondary to a toxic ribonucleic acid (RNA) foci. It sequesters RNA binding proteins, leading to disruption in splicing and transcription of other genes.[3,4] The function of the C9orf72 protein is unclear. Fewer than 30 expansion repeats are documented among controls. Around 90 percent of the people with expansions are diagnosed with either ALS and/or behavioral variant FTD. The lifetime risk of C9orf72 associated with either ALS or FTD is approximately 1 in 2,000.[5] Patients with features of combined ALS and FTD and a family history of either disease have a 50-percent likelihood of exhibiting C9orf72 repeat expansion.

Individuals with the repeat expansions are reported to have a family history of other neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, multiple sclerosis, and Huntington's disease.[5–8] There is no established direct relationship between C9orf72 repeat expansion and the above mentioned neurodegenerative conditions.

A frequent clinical ALS phenotype is of relatively rapid progression, female preponderance, and bulbar dysfunction.[9] Previously, ALS was thought to be a pure motor neuron disease; however, people with ALS also can exhibit cognitive and/or behavioral symptoms. FTD is clinically associated with behavioral changes in personality, of poor judgment, impulsivity, and/or for aphasias. The aphasia may vary from non-fluencies, to word selection difficulties, or to non-recognition of things to which the person previously had been familiar. There is a continuum from pure motor neuron dysfunction ALS to ALS with mild cognitive impairment, to ALS with behavioral impairment, and to ALS comorbid with FTD;[10] similarly, some FTD patients also exhibit motor features of ALS. Thus, C9orf72 repeat expansion may unify both of these diagnoses in an association pattern. Individuals with repeat expansion frequently exhibit behavioral variant FTD. Earlier age onset may be secondary to genetic anticipation, similar to our patient's son in the clinical vignette. The issue of anticipation is unresolved because the exact number of pathogenic repeats has not been established. There is no clinical correlation between increasing repeats and earlier age onset. Hence, genetic anticipation in cases of C9orf72 repeats remains theoretical.

Patients with C9orf72 repeat expansion have TDP-43 cytoplasmic inclusions similar to people with classical ALS.[1,2] There is an association of repeat expansion with ubiquitylated neuronal cytoplasmic

inclusions in the CA4 subfield of the hippocampus, concluding that this pathological finding is a reliable indicator of GGGGCC repeat expansion.[7] There are some encouraging results with antisense oligonucleotides that might target GGGGCC RNA sequences, reducing toxic RNA foci and RNA binding protein sequestration.[3]

Unanswered questions include the function of the C9orf72 protein, genetic anticipation, and the number of pathogenic repeats. Research about antisense oligonucleotide may facilitate better management of ALS-FTD.

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